• Clinical Research •

Subconjunctival trypsin injection for anterior chamber fibrin exudates in eyes with globe rupture following vitrectomy

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Abstract

● **AIM:** To compare the safety and clinical outcomes of subconjunctival trypsin and dexamethasone (DEX) injections in the treatment of anterior chamber fibrin exudates in eyes with globe rupture following primary wound repair and vitrectomy.

● **METHODS:** A retrospective analysis included 42 males and 10 females (mean age 46.0±6.0y, range 34 to 58y) who underwent primary wound sutures and vitrectomy for globe rupture. Patients with pupil-covered fibrinous exudate or/and membrane in the anterior chamber were treated. On the first postoperative day, subconjunctival injections of either 5000 units (0.4 mL) of trypsin solution (n=25) or 0.5 mL (1 mg) DEX (n=27) were administered to accelerate exudate absorption. Efficacy was assessed by observing break time and partial absorption of the fibrin exudate membrane. Safety and comfort were evaluated by monitoring intraocular pressure (IOP), allergy, pain, and foreign body sensation.

● **RESULTS:** Both groups achieved 1/3 absorption of the anterior chamber fibrin exudate membrane, but the trypsin group exhibited shorter break time and partial absorption time compared to the DEX group (P<0.05). Trypsin treatment was also less irritating to patients. No adverse reactions were reported, and IOP remained stable. Visual acuity improved in both groups without statistical difference.

● **CONCLUSION:** Compared to DEX, trypsin demonstrates a shorter absorption time for the fibrin exudate membrane with a more comfortable process in treating pupil-covered fibrinous exudate or/and membrane after vitrectomy for globe rupture.

● **KEYWORDS:** globe rupture; vitrectomy; exudative fibrin membrane; trypsin; dexamethasone

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INTRODUCTION

Open eye injuries, involving full-thickness lacerations of the eye wall, can severely impair vision[1]. Globe rupture due to blunt trauma is a common occurrence in activities such as sports, recreation, altercations, or traffic accidents, often resulting in blindness worldwide[2-3]. The non-compressibility of intraocular structures can lead to rapid elevation of intraocular pressure (IOP) following blunt force

trauma, ultimately resulting in rupture at the weakest point of the eye wall, such as the corneal rim[4]. The primary aim of initial surgical suturing following a rupture injury is to seal the eye, prevent infection and sympathetic ophthalmia, maintain ocular integrity for subsequent examination, and prepare for secondary surgeries[5]. Pars plana vitrectomy (PPV) is commonly performed as a second-stage surgical intervention, typically 3 to 14d post-initial suturing[6]. Prolonged delays in secondary surgery increase the risk of vitreous fibrous proliferation, complicating surgical procedures and impacting patient prognosis. Studies have observed fibroblast growth into the vitreous within three days post-rupture in animal models[7]. PPV is crucial for ongoing management post-severe globe rupture suture[8]. However, severe intraocular inflammation complicates surgical procedures in these patients. Following PPV, patients often develop pupil-covered anterior chamber exudative fibrin membranes, which can delay visual recovery, hinder postoperative examination, and lead to complications such as intraocular lens membrane formation, pupil blockage, adhesions, and secondary glaucoma[9-11].

Current treatment modalities include topical or systemic administration of dexamethasone (DEX), non-steroidal anti-inflammatory drugs, mydriatics, miotics, intraocular tissue plasminogen activator (tPA) injection, and ultrasound therapy[12-13]. While topical DEX, combined with non-steroidal anti-inflammatory drugs and mydriatic/cycloplegic drops, is effective for postoperative inflammatory anterior chamber exudative fibrin membrane, it may not suffice in cases of pupil-covered anterior chamber inflammation or poor patient compliance[14]. tPA, activated by fibrin, effectively dissolves fibrin by converting plasminogen to plasmin, aiding in exudative fibrin membrane removal post-surgery[15-16]. However, potential tPA toxicity, including anterior chamber hemorrhage, pain, blurred vision, and keratopathy, raises concerns[17-18]. Despite ultrasound's efficacy in accelerating fibrin emboli absorption in cerebral hemorrhage, its clinical application for anterior chamber fibrous exudative membranes is limited[19]. Therefore, despite available treatment options, there is a need for safer and more effective therapeutic agents.

Proteolytic enzymes, such as trypsin, have long been used to promote tissue repair. Trypsin, a proteolytic enzyme, has been clinically used for over 50y, exhibiting anti-inflammatory properties, and facilitating rapid recovery from acute tissue damage[20-21]. In tissue repair, trypsin selectively hydrolyzes peptide bonds containing lysine or arginine, digesting denatured proteins into polypeptides or amino acids[22]. It can also enhance plasmin activity when combined with α1-antitrypsin or α2-macroglobulin, promoting microcirculation restoration, reducing inflammation and oxidative stress, and boosting macrophage phagocytic activity to prevent infection[23-25]. Numerous clinical trials have demonstrated the efficacy and safety of trypsin in accidental injuries, surgical and orthopedic injuries, burns, and sciatica[26]. However, there is a lack of corresponding research on the treatment and application of anterior chamber exudative membranes. This study retrospectively analyzes the efficacy and safety of subconjunctival trypsin and DEX injections for treating pupil-covered anterior chamber exudation post-PPV in ocular trauma patients.

SUBJECTS AND METHODS

Ethical Approval This retrospective study obtained informed consent from all patients and received approval from the ethics committee of the First Affiliated Hospital of Zhengzhou University (Approval number: 2022-ky-0249-002), conducted in accordance with the principles of the Declaration of Helsinki.

Patients with globe rupture who underwent PPV and developed pupil-covered anterior chamber exudative fibrin membranes were included. Electronic medical records from January 2021 to December 2021 were screened. Inclusion criteria were patients with eye injuries sutured, exhibiting vitreous hemorrhage, retinal detachment, or choroidal detachment requiring second-stage PPV. All patients underwent PPV one-week post-suturing, and those with pupil-covered anterior chamber fibrin exudate membranes after PPV were included. Exclusion criteria comprised prior vitreoretinal surgery, intraocular surgery within three months, or other vitreoretinopathies.

A single experienced vitreoretinal surgeon performed retinal surgeries using a 23-gauge vitrectomy system. Surgical procedures included vitrectomy, posterior vitreous detachment, peripheral vitrectomy, retinal laser photocoagulation, and silicone oil filling. Subconjunctival injections of DEX or trypsin were administered upon postoperative identification of pupil-covered anterior chamber fibrin exudate membranes. Trypsin was obtained from SPH No.1 Biochemical & Pharmaceutical Co., Ltd (Approval No.H31022018). DEX preparation involved 0.5 mL (1 mg) DEX (Tianjin Kingyork Group Hubei Tianyao Pharmaceutical Co., Ltd) with 0.3 mL lidocaine for subconjunctival injection, while trypsin preparation involved dissolving 25 000 units of trypsin with 2.5 mL lidocaine, using 0.4 mL (5000 units) of the solution for subconjunctival injection. A skin scratch test was performed 15min prior to trypsin injection, and negative results indicated suitability for injection. All patients received once-daily subconjunctival injections.

Primary outcomes included time to partial absorption (break time) and time to 1/3 absorption (1/3 absorption time) of the anterior chamber fibrin-exuding membrane, along with medication comfort indicators (pain and foreign body

sensation). Secondary outcomes included IOP and visual acuity. Patient-reported pain and foreign body sensations, along with clinical examinations using slit lamp and indirect ophthalmoscope, were recorded daily post-injection. Fibrin membrane absorption was monitored daily using slit lamp examination. Break time and one-third absorption time were evaluated to assess the efficacy of the treatment. For each patient, the exact time of membrane rupture and partial absorption was recorded, along with corresponding IOP and visual acuity. Data on pain, foreign body sensations, exudate absorption time, IOP, and visual acuity were retrospectively collected from medical records.

Statistical analysis was conducted using GraphPad Prism (v9.0.1 for macOS) software (GraphPad Software, San Diego, CA, USA). Normality was assessed using the Shapiro-Wilk test. Parametric variables were reported as mean±standard deviation, while non-parametric variables were reported as median values (interquartile range). Categorical variables were expressed as absolute frequencies and percentages. Fisher's exact test analyzed categorical variables, while the Mann-Whitney *U* test and Student's *t*-test compared continuous variables. Repeated-measures ANOVA was used for repeated measures data. Statistical significance was set at $P<0.05$.

RESULTS

Demographics of Patients A retrospective analysis included 52 patients (52 eyes) with globe rupture who underwent PPV and developed exudative membranes (Table 1). Twenty-five patients (20 males and 5 females) with a mean age of 45.4±6.4y received subconjunctival injections of 0.5 mL (1 mg) DEX with 0.3 mL lidocaine, while twenty-seven patients (22 males and 5 females) with a mean age of 46.6±5.7 received 5000 units (0.4 mL) trypsin injections. There were no significant differences in sex (P=1.000) or age (P=0.479) between the two groups. At baseline, the exudative membrane completely covered the pupillary area in all patients. Moreover, the baseline IOP and uncorrected visual acuity (UCVA) in the logarithm of the minimum angle of resolution (logMAR) of the DEX-treated group and the trypsin-treated group were 15.0 (3.5)/15.0 (5.0) mm Hg and 2.7 (0.3)/2.7 (0.3) logMAR. No statistical differences were observed in baseline IOP (P=0.189) or UCVA (P=0.928) between the two groups. Except for choroidal detachment, no significant differences in other clinical features were noted between the groups. There was no significant difference in IOP or visual acuity between the two groups of patients with choroidal detachment, both before and after surgery. Notably, transient IOP elevation occurred in one patient in the trypsin group and two in the DEX group, which resolved after exudative absorption.

Exudative Membrane Absorption and UCVA Improvement UCVA was documented, and the break and 1/3 absorption time

Table 1 Demographics and clinical findings of included participants

n (%)

Parameters	DEX group (*n*=25)	Trypsin group (*n*=27)	*P*
Sex			1.000
Female	5 (20.0)	5 (18.5)	
Male	20 (80.0)	22 (81.5)	
Age (y)	45.4±6.4	46.6±5.7	0.479
Eyes			0.785
Right eye	10 (40.0)	12 (44.4)	
Left eye	15 (60.0)	15 (55.6)	
UCVA (logMAR)[a]	2.7 (0.3)	2.7 (0.3)	0.928
IOP (mm Hg)[a]	15.0 (3.5)	15.0 (5.0)	0.189
IOFB			1.000
Yes	6 (24.0)	6 (22.2)	
No	19 (76.0)	21 (77.8)	
Causative object			1.000
Metallic object	4 (16.0)	4 (14.8)	
Elastic object	1 (4.0)	0	
Stone object	1 (4.0)	0	
Glass object	0	1 (3.7)	
Eyelash	0	1 (3.7)	
Waiting time (h)	19.6±6.3	20.5±5.4	0.606
Corneal wound			1.000
Yes	8 (32.0)	8 (29.6)	
No	17 (68.0)	19 (70.4)	
Corneal wound across pupil			0.315
Yes	2 (8.0)	5 (18.5)	
No	6 (24.0)	3 (11.1)	
Scleral laceration length (mm)	6.8±2.8	8.3±2.8	0.074
Scleral laceration location			0.906
Superior side	2 (8.0)	2 (7.4)	
Inferior side	1 (4.0)	1 (3.7)	
Nasal side	8 (32.0)	6 (22.2)	
Temporal side	14 (56.0)	18 (66.7)	
Retinal detachment			0.422
Yes	23 (92.0)	22 (81.5)	
No	2 (8.0)	5 (18.5)	
Choroidal detachment			0.006
Yes	6 (24.0)	17 (63.0)	
No	19 (76.0)	10 (37.0)	
Vitreous hemorrhage			1.000
Full filled	7 (28.0)	8 (29.6)	
Limited	18 (72.0)	19 (70.4)	
Macular hole			1.000
Yes	1 (4.0)	2 (7.4)	
No	24 (96.0)	25 (92.6)	
Endophthalmitis			1.000
Yes	2 (8.0)	2 (7.4)	
No	23 (92.0)	25 (92.6)	

[a]Data are presented as median values (interquartile ranges) and tested by Mann-Whitney *U* test. Other categorical variables are presented as absolute frequencies and tested by Fisher's exact test; other continuous variables are presented as mean±SD and tested by *t*-test. DEX: Dexamethasone; UCVA: Uncorrected visual acuity; IOP: Intraocular pressure; IOFB: Intraocular foreign body.

of the exudative membrane were observed to assess the direct treatment effect of DEX and trypsin. Following treatment, the exudative membrane covering the pupil area broke in 2.9±0.9d and 1.6±0.7d, achieving 1/3 absorption in 6.3±1.3d and 4.0±1.2d in the DEX and trypsin groups, respectively. Trypsin treatment exhibited significantly shorter break time (P=0.000) and 1/3 absorption time (P=0.000) compared to DEX treatment (Figure 1). Both groups showed significant UCVA improvement due to removal of the light-blocking exudative membrane (Figure 2), with no statistical difference in UCVA between groups (Figure 3A). Furthermore, there was no significant difference in final visual acuity change compared to baseline between the two groups (P=0.372).

IOP Stabilization and Treatment Comfort IOP, pain, and foreign body sensation were monitored to assess treatment safety and comfort. All patients passed the skin scratch test without allergic reactions, and no patients required anti-glaucoma medications. While there was a slight upward trend in IOP at 1/3 absorption, no statistical difference was observed (Figure 3B), and no significant difference in IOP was noted between groups at any time. DEX treatment was associated with a higher incidence of pain (17 painful patients out of 27) compared to trypsin (3 painful patients out of 25, P=0.000). Additionally, fewer trypsin-treated patients reported foreign body sensation (8 out of 25) compared to DEX-treated patients (19 out of 27; P=0.012). No adverse events were documented.

DISCUSSION

This retrospective study demonstrated that subconjunctival trypsin injection significantly accelerated the absorption of anterior chamber fibrin exudates, providing a safe and effective treatment option. Notably, trypsin administration did not lead to allergic reactions or complications such as elevated IOP, ensuring its safety profile. Moreover, patients treated with trypsin reported significantly less pain and foreign body sensation compared to those receiving DEX injections. This discrepancy may stem from differences in injection dose and lidocaine concentration in the drug formulation. While trypsin was dissolved directly with lidocaine, allowing for a smaller injection volume, DEX required a larger volume due to limited lidocaine addition.

In terms of visual outcomes, both trypsin and DEX treatments resulted in significant improvement in UCVA by removing the light-blocking exudative membrane, with no statistical difference between the groups. Additionally, there was no significant difference in final visual acuity change compared to baseline, indicating comparable efficacy between the treatments. Moreover, no significant difference in IOP was observed between the two groups, suggesting that short-term subconjunctival application may not induce IOP fluctuations.

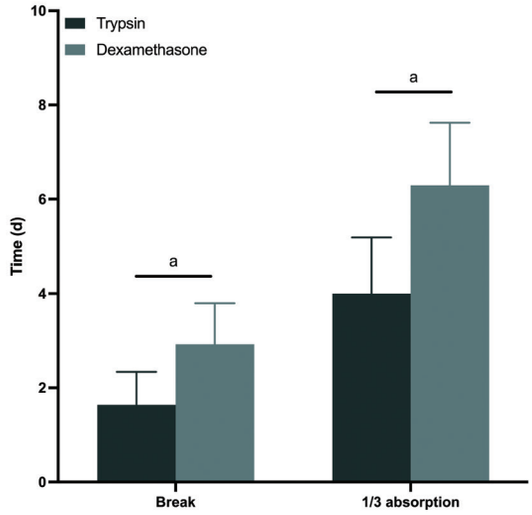

Figure 1 The treated eyes' exudative membrane break and 1/3 absorption time [a]P<0.0001.

Importantly, the cost of both treatments was comparable under China's current medical insurance system.

Choroidal detachment, a condition characterized by fluctuations in IOP, is frequently attributed to trauma. Research indicated that the threshold for inducing choroidal detachment in porcine eyes was a projectile with 2 joules of energy[27]. Furthermore, investigations involving elderly patients with open globe injuries and young children with similar injuries revealed that choroidal detachment was present in 38% and 39% of cases, respectively[2,28].

It is hypothesized that trauma results in a significant impact force exerted on the eyeball wall, leading to its rupture and subsequent tear in the choroid. This tear facilitates the connection between the subretinal and suprachoroidal spaces, resulting in the accumulation of intraocular bleeding within these spaces[29]. Another perspective suggests that trauma-induced eyeball rupture can reduce IOP, leading to a decrease in pressure within intraocular tissues. This reduction can significantly elevate the net driving pressure from capillaries into the interstitial space, ultimately causing fluid accumulation in the affected area[30].

This study identified variations in choroidal detachment among the two patient groups. However, the findings did not reveal any statistically significant differences in IOP before and after surgery. This lack of significance may be attributed to two reasons: 1) imprecise preoperative IOP monitoring in patients with ocular rupture due to corneal edema and inadequate examination coordination; 2) the presence of choroidal detachment and vitreous hemorrhage in patients with ocular rupture, which obscured the reduction in IOP resulting from choroidal detachment. Transient elevation in IOP was observed in one case, possibly due to factors such as partial angle blockage during blood absorption or heightened sensitivity to hormones. However, IOP returned to normal following

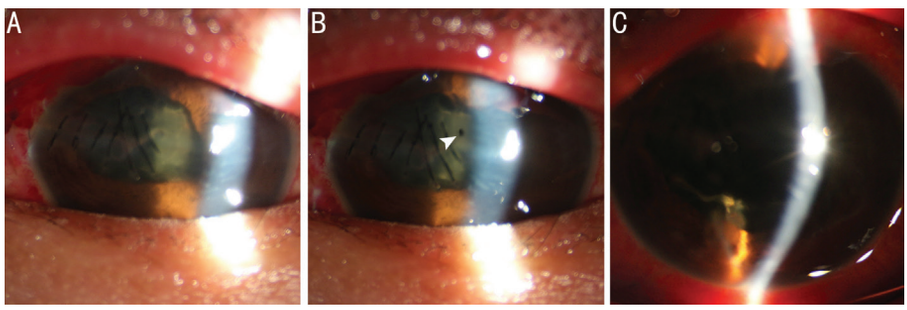

Figure 2 Representative anterior photographs of a patient with severe exudative fibrin membrane in the pupil area at the 1st (A), 3rd (B), and 6th (C) days after the operation White arrowhead: The exudative membrane break.

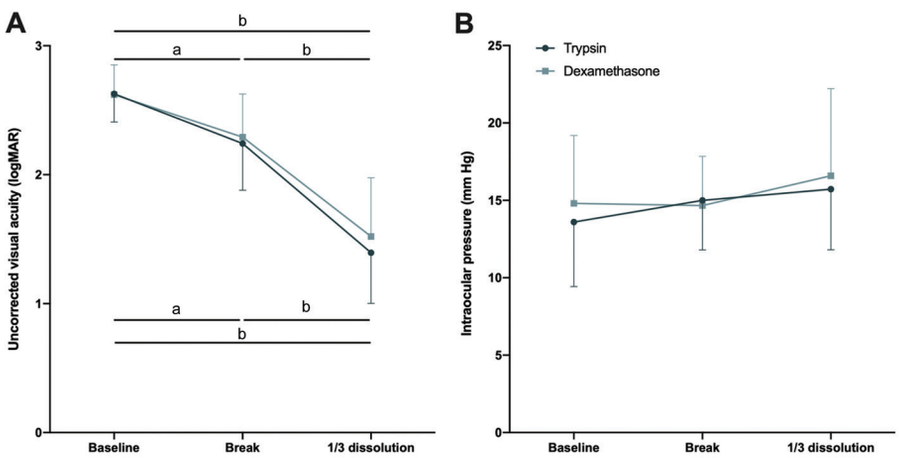

Figure 3 Uncorrected visual acuity and intraocular pressure for treated eyes A: Uncorrected visual acuity for treated eyes. $^{a}P<0.01$, $^{b}P<0.0001$. B: The intraocular pressure of the two groups of treated eyes was not statistically significant.

treatment completion. Notably, no allergic reactions occurred with trypsin use, supported by negative skin scratch tests before treatment. Both trypsin and DEX injections effectively treated pupil-covered anterior chamber fibrin exudates, with trypsin demonstrating faster onset of action and greater treatment comfort.

Formation of fibrin membranes in the anterior chamber following intraocular surgery, inflammation, or anterior segment trauma poses a significant challenge, impacting surgical prognosis. Under normal circumstances, the aqueous humor lacks fibrinogen, preventing active coagulation or inflammation. However, disruption of the blood-aqueous barrier during surgery can induce fibrin-like reactions, leading to fibrin and fibrinogen accumulation[31]. This process, exacerbated by chemokines, induces leukocyte activity and adhesion, exacerbating ocular inflammation[14]. Patients with globe rupture, experiencing severe inflammation and complex surgical procedures, are more prone to developing exudative fibrin membranes in the anterior chamber.

Although corticosteroids are commonly used for anterior chamber exudation, tPA has shown superior efficacy[32-33]. However, corticosteroids exhibit limited effectiveness on pupil-covered anterior chamber exudative membranes, while tPA's widespread use is hindered by potential complications[14]. In contrast, trypsin, a long-standing clinical tool, has been proven safe in treating various tissue injuries, including inflammation and edema[34-35].

The historical origins of protein hydrolytic enzyme preparations can be traced back to 1876[36]. These enzymes exhibit a range of pharmacological properties, including anti-inflammatory, anti-edema, fibrinolytic, immunomodulatory, and analgesic effects. Exogenous proteolytic enzymes are primarily employed to facilitate tissue healing, making them a viable therapeutic approach for acute injuries[25]. Trypsin, a notably significant exogenous proteolytic enzyme, was introduced into clinical practice in the 1960s[26]. Its enzymatic activity includes the hydrolysis of natural or denatured proteins, fibronectin, and mucin into smaller peptides or amino acids[37]. Additionally, trypsin enhances the penetration of antibiotics into targeted lesion sites and aids in drug absorption[38].

Clinically, trypsin has been shown to reduce inflammation and hematoma formation, as well as exhibit antioxidant properties by reducing free radical formation, thereby contributing to the maintenance of redox homeostasis over extended periods. Research indicated that oral trypsin may modulate the body's microenvironment by enhancing fibronectin-induced angiogenesis, neurite extension, and migration activity[39]. Furthermore, trypsin's potential involvement in promoting pulp regeneration in elderly individuals has been identified[40].

In burn patients, the application of trypsin has been shown to reduce tissue edema, inflammation, and oxidative stress, leading to decreased tissue damage and accelerated repair processes[41]. Trypsin can also be utilized for postoperative debridement, wound cleansing, and enhancement of hand incision healing. Essentially, trypsin, as an adjunct proteolytic enzyme, serves as a therapeutic agent for various injuries and inflammatory conditions, facilitating wound debridement and promoting the regeneration of granulation tissue. Trypsin, derived from pig, sheep, or bovine pancreas, is available as a sterile lyophilized powder. It can be administered *via* subconjunctival injection, lacrimal passage irrigation, or as eye drops[25]. While its exact mechanism of action remains incompletely understood, trypsin exerts its therapeutic effects through direct and indirect pathways (Figure 4). Directly, it acts on lesions by breaking down denatured proteins, exhibiting anti-fibrin exudation, anti-inflammatory, and anti-infection properties. Moreover, as a proteolytic enzyme, trypsin selectively decomposes proteins or polypeptides, enhancing the penetration of antibiotics and other drugs into focal areas.

Indirectly, trypsin boosts the phagocytic activity of natural killer cells and macrophages, exerting anti-infective effects[21]. It can also promote macrophage conversion to M2a macrophages, facilitating wound healing[42]. Additionally, trypsin activates proteinase-activated receptor 2, converting macrophages to an anti-inflammatory phenotype and promoting the secretion of interleukin (IL)-10 for anti-inflammatory effects[43]. In an experimentally induced mouse model of colitis, activation of proteinase-activated receptor 2 inhibited pro-inflammatory cytokines production and reduced T-helper cell type 1, thereby reducing cell necrosis[44]. Therefore, trypsin also has a corresponding therapeutic effect in the clinical application of ophthalmic diseases (Figure 5A). In clinical applications, trypsin can dissolve blood clots, fibrin exudation, and necrotic tissue, improve tissue permeability, inhibit edema and inflammatory reactions, and facilitate the rapid diffusion and absorption of local medicinal solutions (Figure 5B).

Acknowledging the retrospective design and the use of UCVA assessment, which may introduce bias due to factors such as silicone oil and trauma influencing refractive status, we emphasize the need for further research on trypsin's efficacy in ophthalmic diseases.

In summary, subconjunctival trypsin injection demonstrates superior efficacy in dissolving exudative fibrin membranes post-PPV compared to DEX. Moreover, trypsin administration in this study did not lead to complications such as elevated IOP or allergic reactions, underscoring its safety. Therefore, we advocate for considering this relatively safe and effective treatment for pupil-covered anterior exudative fibrin

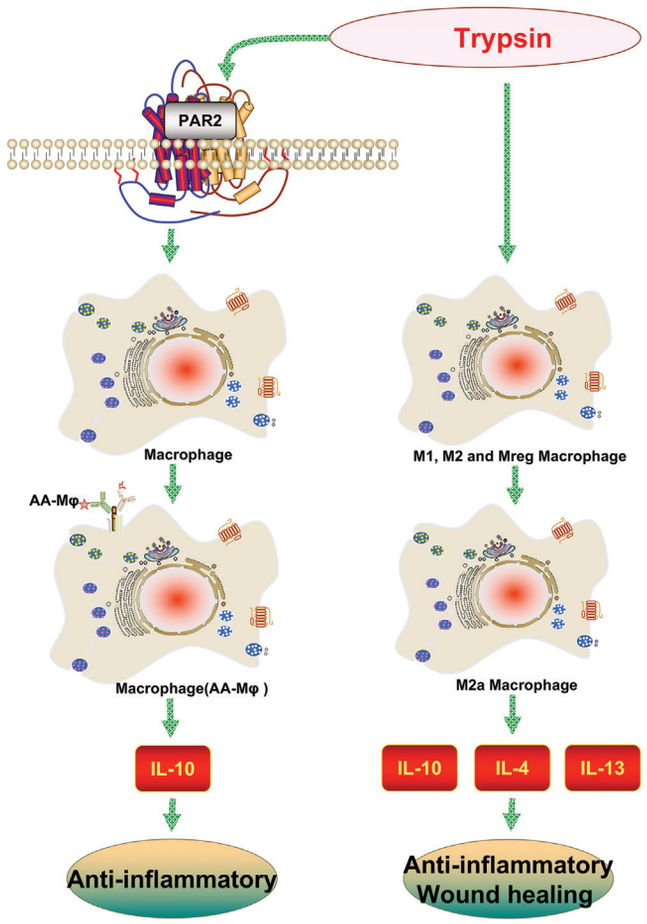

Figure 4 Direct and indirect action of trypsin IL: Interleukin.

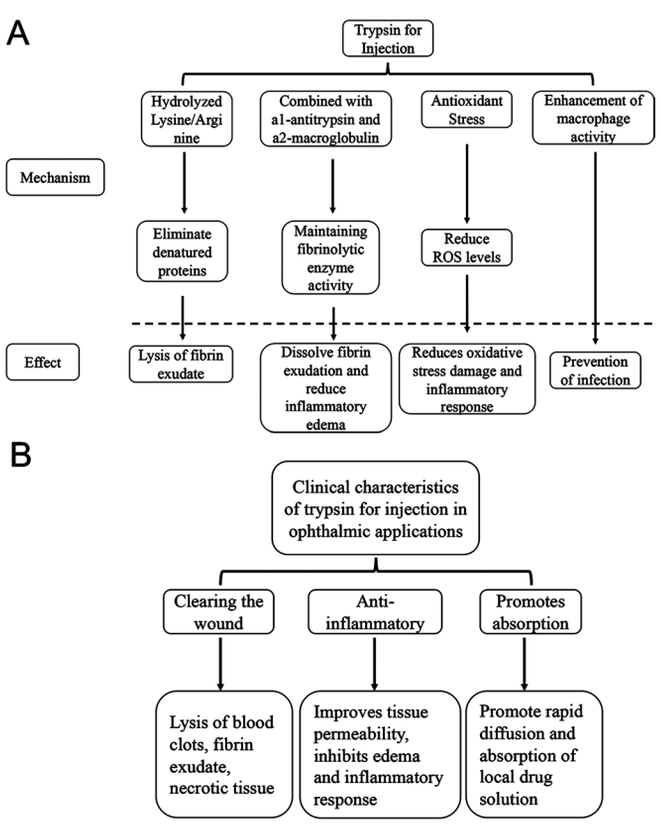

Figure 5 The mechanism and clinical characteristics of trypsin A: Underlying mechanism and effect of trypsin; B: Clinical characteristics of trypsin in treating ophthalmic diseases.

membranes occurring after PPV in trauma patients. As a promising tool in ophthalmology, trypsin warrants further exploration and utilization in various ocular conditions.

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REFERENCES

1 Okamoto Y, Morikawa S, Okamoto F, *et al*. Traffic accident-related open globe injuries. *Retina* 2019;39(4):779-785.

2 Sheng I, Bauza A, Langer P, Zarbin M, Bhagat N. A 10-year review of open-globe trauma in elderly patients at an urban hospital. *Retina* 2015;35(1):105-110.

3 Dulz S, Dimopoulos V, Katz T, Kromer R, Bigdon E, Spitzer MS, Skevas C. Reliability of the ocular trauma score for the predictability of traumatic and post-traumatic retinal detachment after open globe injury. *Int J Ophthalmol* 2021;14(10):1589-1594.

4 Morikawa S, Okamoto Y, Okamoto F, *et al*, Japan-Clinical Research of Study group. Clinical characteristics and outcomes of fall-related open globe injuries in Japan. *Graefes Arch Clin Exp Ophthalmol* 2018;256(7):1347-1352.

5 Joussen AM, Müller B, Kirchhof B, Stappler T, Zeitz O. Rupture of the globe: what to do, what not to do. *Klin Monbl Augenheilkd* 2020;237(9):1070-1078.

6 Coleman DJ. Early vitrectomy in the management of the severely traumatized eye. *Am J Ophthalmol* 1982;93(5):543-551.

7 Cleary PE, Ryan SJ. Histology of wound, vitreous, and retina in experimental posterior penetrating eye injury in the rhesus monkey. *Am J Ophthalmol* 1979;88(2):221-231.

8 Qin ZX, He Y, Xu YF, Yu T, Liu Y, Wu N. Pediatric ocular trauma with pars plana vitrectomy in southwest of China: clinical characteristics and outcomes. *Int J Ophthalmol* 2021;14(9):1321-1326.

9 Siatiri H, Beheshtnezhad AH, Asghari H, Siatiri N, Moghimi S, Piri N. Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery. *Br J Ophthalmol* 2005;89(11):1458-1461.

10 Wu TT, Wang HH. Intracameral recombinant tissue plasminogen activator for the treatment of severe fibrin reaction in endophthalmitis. *Eye(Lond)* 2009;23(1):101-107.

11 Limon U, Sezgin Akçay BI. Efficacy of intravitreal dexamethasone after combined phacoemulsification and pars plana vitrectomy for diabetic tractional retinal detachments. *J Ocul Pharmacol Ther* 2022;38(2):176-182.

12 Reddy S, Tyagi M, Govindhari V. Batman in the anterior chamber: retracting fibrin on anterior segment optical coherence tomography. *Indian J Ophthalmol* 2020;68(9):1972.

13 Ibramsah AB, Cheong AI, Wan Muda WN, Ibrahim M. The efficacy of recombinant tissue plasminogen activator in severe post-operative fibrinous reaction after uneventful phacoemulsification–a case series and review. *Rom J Ophthalmol* 2022;66(1):27-31.

14 Georgiadis N, Boboridis K, Halvatzis N, Ziakas N, Moschou V. Low-dose tissue plasminogen activator in the management of anterior chamber fibrin formation. *J Cataract Refract Surg* 2003;29(4):729-732.

15 Young JB, Buchberger AR, Bogaard JD, Luecke LB, Runquist M, Skumatz CMB, Kassem IS. Tissue plasminogen activator effects on fibrin volume and the ocular proteome in a juvenile rabbit model of lensectomy. *Transl Vis Sci Technol* 2021;10(14):7.

16 Ferguson TJ, Traboulsi EI, Goshe JM. Successful pediatric DMEK facilitated by intracameral tissue plasminogen activator to mitigate anterior chamber fibrin reaction. *Am J Ophthalmol Case Rep* 2020;19:100812.

17 Diez-Iriepa D, Knez D, Gobec S, Iriepa I, de Los Ríos C, Bravo I, López-Muñoz F, Marco-Contelles J, Hadjipavlou-Litina D. Polyfunctionalized α-phenyl-tert-butyl(benzyl)nitrones: multifunctional antioxidants for stroke treatment. *Antioxidants* 2022;11(9):1735.

18 Kimura S, Morizane Y, Toshima S, Shiode Y, Doi S, Takahashi K, Matoba R, Kanzaki Y, Shiraga F. Cytotoxic effects of alteplase, a recombinant tissue plasminogen activator, on human retinal pigment epithelial cells. *Jpn J Ophthalmol* 2021;65(5):731-739.

19 Yamashita T, Ohtsuka H, Arimura N, Sonoda S, Kato C, Ushimaru K, Hara N, Tachibana K, Sakamoto T. Sonothrombolysis for intraocular fibrin formation in an animal model. *Ultrasound Med Biol* 2009;35(11):1845-1853.

20 Yu RC, Bunge RP. Damage and repair of the peripheral myelin sheath and node of Ranvier after treatment with trypsin. *J Cell Biol* 1975;64(1):1-14.

21 Chandanwale A, Langade D, Sonawane D, Gavai P. A randomized, clinical trial to evaluate efficacy and tolerability of trypsin: chymotrypsin as compared to serratiopeptidase and trypsin: bromelain: rutoside in wound management. *Adv Ther* 2017;34(1):180-198.

22 Leiros HK, Brandsdal BO, Andersen OA, Os V, Leiros I, Helland R, Otlewski J, Willassen NP, Smalås AO. Trypsin specificity as elucidated by LIE calculations, X-ray structures, and association constant measurements. *Protein Sci* 2004;13(4):1056-1070.

23 Lackey L, Coria A, Ghosh AJ, *et al*. Alternative poly-adenylation modulates α1-antitrypsin expression in chronic obstructive pulmonary disease. *PLoS Genet* 2021;17(11):e1009912.

24 Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. *Int J Mol Sci* 2018;19(6):1801.

25 Ma C, Li HY, Lu SW, Li X, Wang S, Wang WZ. Tryptase and exogenous trypsin: mechanisms and ophthalmic applications. *J Inflamm Res* 2023;16:927-939.

26 Shah D, Mital K. The role of trypsin: chymotrypsin in tissue repair. *Adv Ther* 2018;35(1):31-42.

27 Sponsel WE, Gray W, Scribbick FW, Stern AR, Weiss CE, Groth SL, Walker JD. Blunt eye trauma: empirical histopathologic paintball impact thresholds in fresh mounted porcine eyes. *Invest Ophthalmol Vis Sci* 2011;52(8):5157-5166.

28 Read SP, Cavuoto KM. Traumatic open globe injury in young pediatric patients: characterization of a novel prognostic score. *J AAPOS* 2016;20(2):141-144.

29 Feng K, Wang CG, Hu YT, Yao Y, Jiang YR, Shen LJ, Pang XQ, Nie HP, Ma ZZ. Clinical features and prognosis of eyeball rupture: eye injury vitrectomy study. *Clin Exp Ophthalmol* 2015;43(7):629-636.

30 Diep MQ, Madigan MC. Choroidal detachments: what do optometrists need to know? *Clin Exp Optom* 2019;102(2):116-125.

31 da Rocha Lima B, Pichi F, Nucci P, Srivastava SK, Lowder CY. Fibrin reaction after uveitic cataract surgery: treatment and prevention. *Eur J Ophthalmol* 2014;24(4):626-628.

32 Gaballa SA, Kompella UB, Elgarhy O, Alqahtani AM, Pierscionek B, Alany RG, Abdelkader H. Corticosteroids in ophthalmology: drug delivery innovations, pharmacology, clinical applications, and future perspectives. *Drug Deliv Transl Res* 2021;11(3):866-893.

33 Mancuso LA, Nadelstein B, Berdoulay A, Spatola RA. Effect of immediate postoperative intracameral tissue plasminogen activator (tPA) on anterior chamber fibrin formation in dogs undergoing phacoemulsification. *Vet Ophthalmol* 2019;22(4):477-484.

34 Brakenbury PH, Kotowski J. A comparative study of the management of ankle sprains. *Br J Clin Pract* 1983;37(5):181-185.

35 Gaspardy G, Balint G, Mitusova M, Lorincz G. Treatment of sciatica due to intervertebral disc herniation with chymoral tablets. *Rheumatol Phys Med* 1971;11(1):14-19.

36 Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application. An update. *J Ethnopharmacol* 1988;22(2):191-203.

37 Huijghebaert S, Vanham G, van Winckel M, Allegaert K. Does trypsin oral spray (viruprotect®/ColdZyme®) protect against COVID-19 and common colds or induce mutation? caveats in medical device regulations in the European union. *Int J Environ Res Public Health* 2021;18(10):5066.

38 Henrotin YE, Michlmayr C, Rau SM, Quirke AM, Bigoni M, Ueberall MA. Combination of enzymes and rutin to manage osteoarthritis symptoms: lessons from a narrative review of the literature. *Rheumatol Ther* 2022;9(5):1305-1327.

39 Iohara K, Zayed M, Takei Y, Watanabe H, Nakashima M. Treatment of pulpectomized teeth with trypsin prior to transplantation of mobilized dental pulp stem cells enhances pulp regeneration in aged dogs. *Front Bioeng Biotechnol* 2020;8:983.

40 Latha B, Ramakrishnan M, Jayaraman V, Babu M. The efficacy of trypsin: chymotrypsin preparation in the reduction of oxidative damage during burn injury. *Burns* 1998;24(6):532-538.

41 Latha B, Ramakrishnan KM, Jayaraman V, Babu M. Action of trypsin: chymotrypsin (Chymoral forte DS) preparation on acute-phase proteins following burn injury in humans. *Burns* 1997;23(Suppl 1):S3-S7.

42 White MJ, Gomer RH. Trypsin, tryptase, and thrombin polarize macrophages towards a pro-fibrotic M2a phenotype. *PLoS One* 2015;10(9):e0138748.

43 Nhu QM, Shirey KA, Pennini ME, Stiltz J, Vogel SN. Proteinase-activated receptor 2 activation promotes an anti-inflammatory and alternatively activated phenotype in LPS-stimulated murine macrophages. *Innate Immun* 2012;18(2):193-203.

44 Fiorucci S, Mencarelli A, Palazzetti B, *et al*. Proteinase-activated receptor 2 is an anti-inflammatory signal for colonic lamina propria lymphocytes in a mouse model of colitis. *Proc Natl Acad Sci U S A* 2001;98(24):13936-13941.